REMARKS

Amendments to the Specification were made at page 1 to update the status of the priority applications. The Specification is amended on pages 8, 86, 89 and 141-142 to update the address of the American Type Culture Collection (ATCC) which has been relocated.

Typographical/proofreading errors have been corrected at pages 13, 16, 26, 54, 91, 94-96, 98, 107 and in TABLE 2 on page 131, and the SEQUENCE LISTING has been inserted at the end of the specification after page 143.

Claims 1-30 have been cancelled, and new Claims 31-46 have been added. Applicants respectfully submit as supported below that no new matter has been entered by the amendments to the Specification or by the addition of new claims 31-46.

Amendments to the Specification at pages 27-28

The Specification has been amended at page 27, line 20 to correct the description of Figure 15 to be consistent with the replacement Figures 15A-C. Those changes were made necessary to correct the MN cDNA sequence and the MN amino acid sequence deduced therefrom. As explained in the copy of the accompanying Declaration Concerning MN cDNA Sequence and Amino Acid Sequence Deduced Therefrom with attached Appendices 1 and 2 which was submitted in the parent application, U.S. Serial No. 08/260,190 (now allowed), the Applicants made errors in sequencing the MN cDNA primarily due to nonapparent compression of nucleotides,

which were initially unrecognized. The indicated sequence corrections were made in the now allowed parent application.

Applicants respectfully submit that the patent case law allows for the correction of the MN cDNA and amino acid sequences (SEQ ID NOS: 1, 2, 5 and 6) under the circumstances pertaining to the instant application. Such corrections are not considered to be new matter in accordance with the case law.

A PTO 1979 Board of Appeals decision -- Ex parte Marsili, 214 USPQ 904 (PTO Bd. App. 1979) -- stands for the proposition that a change in structural formula of a chemical compound that was adequately described in terms of its characteristics in an original specification does not violate the description requirement of 35 USC 112. As detailed above, the MN cDNA sequence, which was discovered and isolated by the Applicants, was missequenced at some points. Those errors were not recognized until after the filing date of the parent application, U.S. Serial No. 08/260,190.

Applicants respectfully submit that those sequencing errors can now be rectified in accordance with Ex parte Marsili, supra. The PTO Board of Appeals stated in that case at pages 906-907:

> [T]he products described, exemplified and claimed by Appellants inherently had and have now the structure given in the amendment in question. Consequently, the changes made in the amendment do not constitute new matter.
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> . . . .
>
> Also compelling in its logic is the observation by the CCPA in still another

> decision involving proper identification of new compounds (Petisi et al. v. Rennharel et al., . . . 150 USPQ 669; 1996):
>
> > "The *product*, not the formula or name, is the invention," . . . .
> >
> > The PTO exists to carry out the job assigned it by Congress, pursuant to the Constitution (Article I, Section 8), i.e. to issue patents which "promote the Progress of Science and useful Arts." To refuse correction of the structural formula of Appellants' claimed compounds, which have been found patentable by the Examiner, would lead to the absurdity of issuing a patent which teaches the public in its specification the wrong scientific formula for the new products.

[Italicized emphasis in original; underlined emphasis added.]

The PTO Board of Patent Appeals and Interferences in Ex parte D, 27 USPQ2d 1067 (PTO Bd. App. & Interf. 1993) cited to Ex parte Marsili approvingly at page 1070, noting at page 1069 that while the precedential decisions allowing the correction of errors in structural formulae

> refer to chemical compounds, rather than sequenced DNA, we stress that a gene is a chemical compound, albeit a complex one. See *Amgen Inc. v. Chugai Pharmaceutical Co.*, . . . 18 USPQ2d 1061 (Fed. Cir. 1991), at 18 USPQ2d 1021. Thus, it is manifest that the prior decisions involving chemical compounds are equally applicable to claims directed to the present subject matter.

The Board went on in Ex parte D to hold that "'routine experimentation' may involve rather extensive studies without straying from 'undue' experimentation, and . . . we are satisfied that the [sequence] changes in the application of the Goeddel

patent were of the type condoned by the decisions in *In re Magerlein, supra* and In re *Nathan, supra*."[1]

Applicants respectfully distinguish the instant case from that of Ex parte Maizel, 27 USPQ2d 1662 (PTO Bd. Pat. App. & Interf. 1992). In the instant case, the deposit at the ATCC of the hybridoma, that produces the M75 monoclonal antibody, enables one of skill in the art to isolate cDNA expressing MN protein that can be sequenced according to conventional protocols, and to isolate MN protein per se that can be sequenced.

Applicants respectfully submit that given the M75 antibody disclosed in the grand-parent application, U.S. Serial No. 08/177,093 [filed December 30, 1993; now U.S. Patent No. 6,051,226] and the hybridoma for which was deposited at the ATCC, ones of skill in the art of expression cloning, protein isolation and sequencing would be able to isolate the MN cDNA and/or MN protein, and to sequence that cDNA and/or protein to obtain the correct MN cDNA and amino acid sequences. The great grand-parent application, U.S. Serial No. 07/964,589 [filed October 21, 1992; now U.S. Patent No. 5,387,676 ("the '676 patent")] and the parent application (U.S. Serial No. 08/260,190) enable one of skill in the art to determine the correct MN cDNA and amino acid sequences

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1. Ex parte Marsili, supra refers to In re Nathan, 140 USPQ 601 (CCPA 1964) and Riester v. Kendall, 72 USPQ 481 (CCPA 1947) as leading cases on the point that corrections can be made to structural formulae of chemical compounds. In re Nathan held that an amendment providing such a change had not introduced new matter but was "merely a statement of an inherent property of the steroids as disclosed in appellants' original disclosure."

in view of their disclosure, the VU-M75 hybridoma deposited in conjunction with the filing of the great grand-parent application ('676 patent), and conventional prior art methods. A determination of the correct MN cDNA sequence could be made by expression cloning, isolating and sequencing the relevant cDNA. A determination of the correct amino acid sequence could be made either directly by isolating, purifying and sequencing MN protein, or by deducing the amino acid sequence from the MN cDNA sequence.

Exemplary of conventional amino acid sequencing methods is the Edman degradation method described in the textbook by Stryer, Biochemistry [2d edition; Freeman Press, New York; 1981]. Specifically, starting on page 21 of the Stryer textbook, methods are described for determining an amino acid sequence from a sample of pure protein.

The M75 monoclonal antibody is disclosed in the '676 patent as MN-specific. As exemplified therein, the M75 monoclonal antibody can be used to immunoprecipitate MN protein from cell extracts, for example, from HeLa cells grown in dense culture or infected with MX [now identified as lymphocytic choriomeningitis virus (LCMV)]. The M75 monoclonal antibody can then be used to purify MN protein.

Once one of skill in the art had purified MN protein, sequencing of the protein can be accomplished using conventional methods, for example, as outlined in the Stryer textbook. Further, Stryer notes that automated methods for protein

sequencing are in use (for example, on page 27), which simplify the process and are now routine in the art.

Alternatively, the correct amino acid sequence for the MN protein could be determined using the M75 monoclonal antibody by expression cloning of MN cDNA. Such expression cloning using antibodies is described in Sambrook et al., Molecular Cloning A Laboratory Manual, Cold Spring Harbor Laboratory Press, volume 2, chapter 12 (1989). "Immunological methods can, in principle, be used to detect any protein for which a specific antibody is available." [Sambrook et al., page 12.2] Sambrook et al. state three criteria which indicate that an antibody is useful in expression cloning. Those criteria are met by the M75 monoclonal antibody.

First, such antibodies react with the protein of interest on Western blots. Second, such antibodies specifically immunoprecipitate a protein of the expected size from translation of the cDNA under study; and third, such antibodies show weak or undetectable signals when reacted with vectors which do not contain the cDNA of interest.

Applicants respectfully submit that the M75 antibody meets all 3 of the criteria set forth in Sambrook et al. for use in identifying MN-expressing recombinants. First, the great grand-parent application (now the '676 patent) and the instant application discloses the M75 monoclonal antibody as recognizing MN protein in Western blots. Example 2 of the '676 patent and the instant application, demonstrates that the M75 monoclonal

antibody reacts with a protein of the expected size as MN, namely 54/58 kd. Next, Example 6 of the '676 patent and of the instant application, shows experiments in which cell extracts were immunoprecipitated using the M75 monoclonal antibody and electrophoresed on PAGE gels. As with Western blots, the size of the labeled protein was as expected for MN. Third, Example 6 of the '676 patent and of the instant application also shows results of studies in which extracts from tumorigenic cells reacted with the M75 monoclonal antibody, but that extracts from nontumorigenic cells did not. Applicants respectfully assert that those studies are the equivalent to the third criterion of Sambrook et al.

Sambrook et al. states: "Both polyclonal antisera and monoclonal antibodies can meet the above criteria, and both have been used successfully to identify recombinants that express cloned sequences of interest." [Id., at page 12.12.] Protocols for expression cloning using antibodies are included in Chapter 12 of Sambrook et al.

Once a colony of recombinant bacteria are identified by the M75 monoclonal antibody, Applicants respectfully submit that a worker of ordinary skill in the art would then be able to amplify the clone(s) so identified, extract the cDNA therefrom, and sequence the cDNA to obtain the correct sequence of MN cDNA. Chapter 13 of Sambrook et al. details a number of conventional sequencing methods known to those in the art, such as, the Sanger

method of dideoxy-mediated chain termination, and the Maxam-Gilbert chemical degradation of DNA method.

Thus, Applicants respectfully submit that the disclosure of the M75 antibody and its deposit at the ATCC enable a worker of skill in the art to isolate, purify, and sequence both MN amino acid and cDNA sequences. Therefore, Applicants respectfully conclude that in accordance with applicable case law as set forth above, no new matter is entered by correcting both the partial and full-length MN cDNA sequences (SEQ ID NOS: 1 and 5) and the partial and full-length MN amino acid sequences deduced therefrom (SEQ ID NOS: 2 and 6) by the above amendments to the Specification and Drawings.

Replacement of the Word "Increase" with the Word "Decrease" at Page 119, Line 25

For the correction at page 119, line 25, it can be seen in Figure 3 and the description of Figure 3 at page 24, lines 12-17, the antisense oligonucleotides inhibited MN protein (p54/58) expression in lanes A, B and C in comparison to the control lane D. Although Figure 3 shows that the most inhibition (40%) occurred in lane B, that lanes A and B show a 25-35% inhibition of p54/58 expression. Applicants therefore respectfully submit that it is clear from the context of Example 10 (page 118, line 21 to page 120, line 12) in combination with Figure 3 and its description, that the use of the word "increase" at page 119, line 25 was in error and should have read "decrease".

Support for Claims 31-46

Claims 1-30 have been cancelled and new claims 31-46 have been added. Support for claims 31-46 can be found throughout the specification. For example, support for claims 31-40 concerning MN antisense constructs and their use appears at the least at page 5, lines 1-21; at page 15, lines 3-14; at page 36, line 1 to page 37, line 11; at page 92, line 1 to page 94, line 8; and at page 151, lines 20-22. Exemplary support for antisense vectors appears at the least at page 65, line 9 to page 67, line 9, and at page 94, lines 9-11, wherein an antisense MN cDNA/MN promoter construct used to transfect CGL3 cells is described. At page 52, line 14 to page 57, line 6, the specification describes vectors, primarily vectors for recombinant production of MN proteins and polypeptides; and particularly at page 53, line 18 to page 54, line 1, describes the use of recombinant vectors to produce "additional recombinant nucleic acid molecules as a source of MN nucleic acid and fragments thereof."

Support for the antibody claims of claims 41-46 can be found at least at page 81, line 13 to page 91, line 23. More specifically, support for claim 41 wherein the MN-specific antibody is designated to be polyclonal can be found at least at page 12, lines 1-4, at page 80, lines 11-18, at page 81, line 22 to page 82, line 15, at page 82, lines 2-24, at page 83, lines 6-12, among other support.

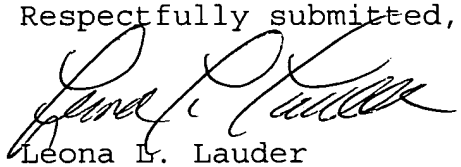
Specific support for claim 44 wherein the MN-specific antibody is humanized can be found at least at page 83, line 15 to page 84, line 16, at page 85, lines 1-9, at page 91, lines 4-5 and at page 91, lines 12-14.

Applicants respectfully conclude that no new matter has been entered by the above amendments and new claims 31-46.

CONCLUSION

Applicants respectfully submit that no new matter has been entered by the above amendments and the addition of new claims 31-46 and request that they be entered for the instant application. If the undersigned Attorney for the Applicants can be of any assistance in regard to this Preliminary Amendment, she can be reached at (415) 981-2034.

Respectfully submitted,



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